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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,590	07/12/1999	BJARNE DUE LARSEN	55508 (45487)	5316

7590 05/15/2002

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	28

DATE MAILED: 05/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/341,590	Applicant(s) LARSEN, BJARNE DUE	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-32 and 52-72* is/are pending in the application.

4a) Of the above claim(s) *13-18,21-23,27,28,62,69,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 27 (filed 2/5/02), claims 3-5 and 37 have been cancelled, claims 1, 24, 29, 52, 54, 57, 62, 64, 68 amended, and claims 69-72 added. Claims 1, 2, 6-32, 52-72 are pending. Claims 13-18, 21-23, 27, 28, 62, 69, 71, 72 are withdrawn from consideration, since they do not encompass the elected specie. Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70 are examined in this Office action.

Applicants' arguments filed 2/5/02 have been considered and found persuasive in part. The previously imposed §102 rejections are withdrawn.

※

A substitute specification is required. Applicants have requested numerous amendments to the specification. These are too numerous for entry. Accordingly, A substitute specification is required. Applicants have misinterpreted this to mean that **if** new sequence listings are submitted, **then** a new substitute specification will be required, and that if new sequence listings are not submitted, a substitute specification will not be required. However, while it is maintained that new sequence listings are required, a substitute specification would be required *even if applicants were in full compliance with the sequence rules*. Thus, regardless of what actions are ultimately taken by applicants or examiner, a substitute specification will be required.

※

This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 with regard to the sequence disclosures.

As indicated previously, further sequence listings are required. The claims encompass conjugates in which "X" can be any of the following:

> enkephalin, Leu-enkephalin, Met-enkephalin, endothelin, vasoactive intestinal peptide, substance P, neurotensin, endorphin, insulin, gramicidin, paracelsin, delta-sleep inducing peptide, angiotensin-I, angiotensin-II, angiotensinogen, angiotensinogen, vasopressin, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide-II, parathyroid hormone (1-34), parathyroid hormone related peptide, EMP-1, atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide (1-53), "mini-ANP", cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin-I, atriopeptin-II, atriopeptin-III, deltorphin-I, deltorphin-II, vasotocin, bradykinin, dynorphin, dynorphin-A dynorphin-B, GRH, GH releasing factor, GH releasing peptide, growth hormone, tachykinin, ACTH, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, leupeptin, sandostatin, galanin, gastric releasing peptide, gastric inhibiting polypeptide, glucagon, glucagon-like peptide -1, glucagon-like peptide-2, exendin-3, exendin-4, LHRH, melanin concentrating hormone, melanocyte stimulating hormone, alpha-MSH, morphine modulating peptide, somatostatin, substance K, TRH, Kyotorphin, melanostatin, hirulog, hirulog-1, melanotan-II, thymosin alpha-1, ornipressin, octreotide, motilin, neurokinin-A, neurokinin-B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, PACAP, pancreatic polypeptide, peptide YY, peptide histidine methionine amide, secretin, thrombopoetein, insulin-like growth factor-I, insulin-like growth factor II, GHRP-6, interleukin-II, beta-interleukin-I, beta-interleukin-II, epidermal growth factor (20-31), eptifibatide, endomorphin-1, endomorphin-2, adrenomodulin, antiarrhytmic peptide, antagonist G, indolicin, osteocalcin, cortistatin-29, cortistatin-14, PD-145065, PD-142893, fibrinogen binding inhibitor peptide, leptin 93-105, GR 83074, and Tyr-W-MIF-1.

A sequence listing has been provided for many of these; however, applicants have failed to provide a sequence listing for all of them. A sequence listing is required for each of the foregoing peptides (that has not already been provided). The sequence listing will aid in the search.

The primary issue pertains to the following phrase in one or more of the claims:

"or a modified **fragment** thereof".

Applicants have argued that they have amended claim 68. However, the claim still encompasses fragments. The sequence listing requirement is maintained.

Applicant is given the time period set in this letter within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 66-67 are drawn to a method of inhibiting neurons from transmitting pain impulses to the spinal cord. There is no evidence that even one of the claimed compounds has any effect one way or another on any neuronal cells. Moreover, there are neuronal cells throughout the body; even if it were true that it were possible to inhibit the neurotransmission between nerves in e.g., the hand and neurons in the spinal cord, why would one expect to

inhibit neurotransmission between nerve cells in the brain and neurons in the spinal chord? And on what basis are applicants asserting that only the transmission "pain" impulses is inhibited; what about the sensations of temperature changes, and merely (non-painful) touch...? Why are these not inhibited as well? It appears that the claims encompass a method of inducing analgesia. It is noted that binding between enkephalin conjugates and μ opioid receptors is described on page 81 of the specification. However, it is not established that such binding will be consequential, even *in vitro*. Does the binding result in stimulation of the receptor, and what are the manifestations? Even the expenditure of "undue experimentation" is unlikely to yield useful data. It is suggested that the claim be amended to recite a method of binding μ opioid receptors. One option is the following:

> *A method of achieving binding between the conjugate {as recited} and μ opioid receptors comprising administering to a subject in need thereof the conjugate for a time an under conditions effective to achieve binding between said conjugate and μ opioid receptors.*

On the other hand, if there is evidence that the μ opioid receptors are somehow "stimulated", it is suggested that evidence to this effect be provided.

Each of the independent claims is drawn to a "pharmacologically active peptide conjugate" that comprises "X" and "Z". While it is certainly true that there are numerous "pharmacologically active" peptides that could correspond to substituent variable "X", it is not necessarily the case that the resulting conjugate will be "pharmacologically active".

Moreover, the term "pharmacologically active" could be viewed as encompassing an assertion of therapeutic efficacy. However, therapeutic efficacy is not in evidence. In addition, the term "pharmacologically active" could potentially encompass therapeutic efficacy of virually any disease, such as Alzheimer's, AIDS, diabetes, cancer, arthritis, cardiovascular diseases, etc. None of this is in evidence. What is suggested is that the phrase "pharmacologically active" be deleted at each occurrence where it occurs immediately preceding "peptide conjugate". One or more of the following claims could be added as well (provided that the term "composition" is not preceded by the term "pharmaceutical"):

A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to bind μ opioid receptors.

A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to stimulate erythropoiesis.

A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to induce retraction of osteoblasts.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims now recite that "X is heteropolymeric" and that "Z comprises at least two

identical amino acid units". However, there does not appear to be support for either of these limitations. Certainly, there are examples of peptides in which these limitations happen to be met. However, it is not apparent that there is a description of these limitations. Applicants are requested to point to the relevant page and line number.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims are drawn to a "pharmacologically active peptide conjugate". As such, the claims are indefinite as to the objectives or manifestations of the pharmacological activity.

- Claim 1 is drawn to a conjugate that comprises "X and Z". Given that the claims now mandate that the N-terminus of Z is bonded to the C-terminus of X, it is suggested that the claim be drawn to a conjugate of the formula "X-Z", as this will improve clarity. A format such as the following could be used:

  A peptide conjugate comprising the formula

  X-Z

  wherein X is a pharmacologically active peptide... ;

  Z is a stabilizing peptide ... ;

  and wherein the alpha-amino group of the N-terminal amino acid of Z is covalently bonded to the alpha-carboxyl group of the C-terminal amino acid of X...; etc.

- Claim 1 recites (last line) "at least about 2". This renders the claim indefinite as to the lower limit. Is the lower limit 2, or is the lower limit less than 2...? It is suggested that the "about" qualifier be deleted. Applicants have argued that the term "about" is not indefinite. The examiner will stipulate that this may be true in general; however, this ground of rejection is directed solely at the use of the term "about" when used to describe a range. When used in this way, a conflict is generated between the lower limit mandated by the range, and the lower limit permitted by "about"; similarly, a conflict is generated between the upper limit mandated by the range, and the upper limit permitted by "about". This rejection applies to all claims reciting the phrase "at least about", or "consists of at the most about".

- The independent claims recite the phrase "having a reduced tendency towards enzymatic cleavage". This renders the claims indefinite. What is the "reduced tendency" relative to? It is suggested that the phrase at issue be deleted.

- In claim 19, second to last line, "bound" should instead be - - bonded - -.

- Several of the claims recite "SEQ ID NO. X", where "X" is an integer. Here, a semicolon should be used, rather than a period, i.e., the following:

SEQ ID NO: X

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject

matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, 70 are rejected under 35 U.S.C. §103 as being unpatentable over Docherty (*Antimicrob Agents Chemother* 31, 1562, 1987) or Burger (*J. Biol. Chem.* **193**, 13, 1951).

As indicated previously, each of Docherty and Burger teach that polylysine exhibits antiviral properties. The references teach that, while the efficacy may be dependent on the chain length, the efficacy can be observed in a variety of chain lengths. Accordingly, polylysine can be viewed as a "conjugate" between one polylysine and another, i.e., $(Lys)_n$ can be viewed as a "conjugate" between $(Lys)_m$ and $(Lys)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p".

The claims now recite that variable "X" must be "heteropolymeric". While this may overcome the §102 rejection, the claims remain obvious nevertheless. The reason is that the term "heteropolymeric" could be interpreted to mean, in the case of e.g., polylysine, that if a single lysine side chain were extended by one methylene unit, or if one methylene unit were removed from the side chain, a "heteropolymeric" peptide would result. Letting "Orn" represent ornithine, and "APG" represent aminopentylglycine, either of the following

would be "heteropolymeric" peptides:

Lys-Lys-Lys-**Orn**-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys

Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-**APG**-Lys-Lys-Lys-Lys-Lys

At the same time, both of these are obvious over the corresponding homopolymeric peptides. The question is not whether one would have expected an improvement over the corresponding homopolymer by adding or deleting a methylene unit; rather the question is whether one would have expected equivalence *a priori*. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)]. As such, the claims are rendered obvious.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, 70 are rejected under 35 U.S.C. §103 as being unpatentable over Sumner-Smith (USP 5,646,120).

As indicated previously, Sumner-Smith teaches that poly-arginine inhibits HIV replication. See, for example, col 6, line 15-20. Thus, $(Arg)_n$ can be viewed as a "conjugate" between $(Arg)_m$ and $(Arg)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p". (Claim 68 is encompassed because of the phrase "or a modified or truncated fragment thereof").

The arguments presented above apply here as well (the §103 over Docherty or Burger). The claims are rendered obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton [phone number (703)308-3213].

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600